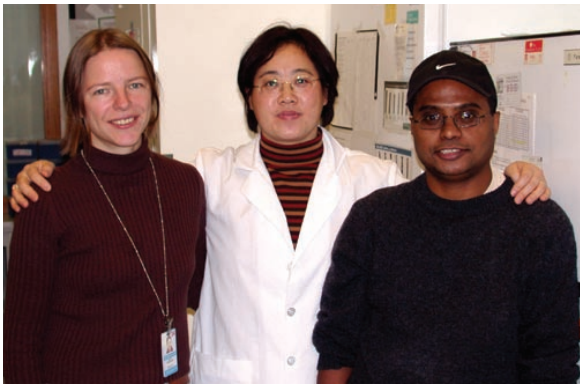
A Brain Cell Gateway

New protein structure may lead to therapies for neural conditions

At the National Synchrotron Light Source (NSLS), scientists from Columbia University have determined the crystal structure of a cell membrane protein that transports glutamate, a chemical essential for normal human brain development and function, in and out of brain cells. This structure has helped them explain how glutamate enters and exits brain cells, which may help researchers develop treatments for neural conditions based on glutamate dysfunction, such as Alzheimer's disease and depression.



Columbia Researchers Olga Boudker, Yan Jin, and Dinesh Yernool

"Until now, there was no information on the three-dimensional structure of a glutamate transport protein or the mechanisms it uses," said Columbia biochemist Eric Gouaux, who led the study. "This structure gives us a very good idea of how the transporter functions."

Glutamate is one of the most important signaling molecules that is transmitted between brain cells, or neurons. These chemical "messengers," called neurotransmitters, enter and exit a neuron by crossing the membrane, a cell's outer skin, via a transporter protein situated within the membrane.

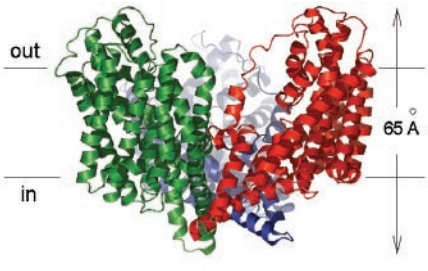
To understand how these transporters function, scientists must first determine their three-dimensional structures. The researchers determined that the glutamate transport protein's structure – the first-ever structure of a neurotransmitter transporter – is bowl-shaped. The bowl, which is filled with a watery solution, is nestled into the membrane such that the basin dips about midway into the membrane and the rim rises just above it.

The bowl's major structural elements are three wedge-shaped segments. The wide ends of each wedge form the rim of the bowl, while the pointy ends meet to form the basin. Each wedge has an intricate sub-structure, composed of multiple helix-shaped protein strands, called "alpha-helices," that are folded and twisted together. These include two helical, hairpin-shaped substructures (hairpins 1 and 2) that are key players in the transport mechanism.

Hairpin 1 is located at the bottom of the basin. Positioned approximately vertical, it spans the thickness of the bowl such that its curved end points up. Hairpin 2 is closer to the rim of the bowl and is connected to hairpin 1 horizontally, with the two curved ends touching, forming a hinge with an inverted "L" shape. Additionally, a large portion of hairpin 2's surface area touches the solution inside the basin.

Gouaux and his team think that hairpin 1 can unhinge from hairpin 2 and swing away from it, like a gate. When glutamate from a neighboring neuron enters the basin and diffuses down through the solution, the gate opens and the glutamate molecule slips through. Together, the three gateways – one in each wedge – make up the glutamate passage system.

"We now have a much better idea of how glutamate is transported into a cell, which gives us more information on how neurons communicate," said Gouaux. "In turn, we may be able to use this information to help find treatments for neural diseases and conditions that are based on glitches in glutamate transport."



The structure of the cell membrane protein, from a view parallel to the cell membrane.

The researchers made these findings at NSLS beamlines X4A, X6A, X25, and X26C. Using a method called protein crystallography, they scattered x-rays off a crystal sample of the transport protein. The scattered x-rays were collected by a detector and then analyzed by a computer, yielding a three-dimensional model of the protein. This research is funded by the Howard Hughes Medical Institute and the National Institutes of Health.

—Laura Mgrdichian